Restriction Requirement:

Restriction to one of the following inventions has been required under 35 U.S.C. § 121:

I. Claims 1-11, 14, 27-29, 31, 32, 36 and 37, drawn to protein and pharmaceutical composition;

II. Claims 12, 13, 15-26, 30 and 35, drawn to DNA, vectors, host cells and method of making protein recombinantly;

III. Claim 33, drawn to method of inhibiting dissemination of tumor cells;

IV. Claim 34, drawn to method of treating arthritis; and

V. Claims 38 and 39, drawn to antibody.

On September 13, 1991, the undersigned elected Group II, with traverse, in a telephone conversation with the Examiner. This election, with traverse, is hereby confirmed.

35 U.S.C. 112

Claims 15 to 22, 25, 26 and 30 are rejected under 35 U.S.C. 112, first paragraph because it is alleged that the disclosure is enabling only for the specific DNA sequences of the application, namely the DNA contained in the vectors p1156HMI2, pYEαG4-HMI, and pDSFα2-MI. It is stated that it would require undue experimentation to practice the invention with other DNA sequences. Applicants respectfully suggest that one could insert other coding sequences into the expression systems of the present invention by the methods described in the application as well as those methods known to one of ordinary skill in the art. Furthermore, it is clear in the claims, as amended, which DNA sequences would fall within the scope of the claim. The DNA sequences must code for a protein that contains some or all of the sequence of the metalloproteinase inhibitor of the present invention and the protein so expressed must have one or more of the biological activities of naturally occuring metalloproteinase inhibitor. Claims 15 to 22 are drawn to the coding portion of the a DNA sequence and therefore do not require the expression and regulatory elements. These claims are drawn to a

purified and isolated DNA sequence that codes for an active human metalloproteinase inhibitor. Claims 25 and 26 are drawn to vectors and hosts for microbial expression. It is submitted that once a coding region is determined, the expression of that coding region can be accomplished in a number of expression systems besides the ones actually used in the present invention. In the present application, three vectors in three species were constructed and all showed successful expression, thereby suggesting that expression is not unpredictable as is asserted by the Examiner. It is therefore submitted that the disclosure is enabling for any coding sequence that codes for a protein having the biological activity of metalloproteinase inhibitor.

Claims 12, 13, 15 to 26, 30 and 35 stand rejected under 35 U.S.C. 112, first and second paragraph, as being vague or inadequaely enabled because of the use of functional language. It is stated that the phrase "primary structural conformation" in claims 12, 13, 25, 26, 30, 15 to 22, and 30 is vague. One skilled in the art would clearly know that primary structure relates to "the covalent backbone structure of polypeptide chains, including the sequence of amino acid residues" [Lehninger, Biochemistry, Worth Publishers, New York (1975) at page 95; also see page 10, lines 6 to 7 of the present application]. It is well established patent law that the claims must be read in light of the specification; in the present application, amino acid sequences for metalloproteinase inhibitors are provided in Figures 1 and 2. It is also stated that the term "biological properties" is also vague in claims 12, 13, 25, 26, 30, 15 to 22, and 30. One skilled in the art would clearly know that biological activity includes in vitro activity and immunological activity that relates to the interaction of the metalloproteinase inhibitor with another molecule, e.g., receptor binding, metalloproteinase inhibitor activity, provocation of the formation of specific antibodies in immunologically active animals. Such functional characteristics as to activity are known to be distinct from, for example, physical characteristics as to the structure of a protein. This interpretation is supported in the present application at page 10, lines 8 to 9, page 11, lines 26 to 31, page 12, lines 11 to 24 and page 17, lines 1 to 23.

It is also stated that the term "including codons preferred for expression" in claims 19 and 21 is vague. Attention is drawn to page 8, line 29 to page 9, line 11 and the methods of Alton et al., PCT published application WO 83/04053. It is therefore submitted that one skilled in the art would know which codons would be preferred by various expression hosts and that there is no vagueness as to such a term.

It is also stated that the term "polypeptide fragment" in claims 23 and 24 is vague. It is also stated that the term "polypeptide analog" in claims 23 and 35 is vague. Both of these terms are described and discussed in the specification at page 10, line 33 to page 12, line 28. The construction of such DNA fragments is known to those of skill in the art. Furthermore, it is stated that such DNA fragments will code for polypeptides having one or more biological activity of metalloproteinase inhibitor and the methods for determining such biological activity are clearly spelled out in the specification. Therefore, one of skill in the art could construct DNA fragments and sequences that would code for polypeptides and then screen those polypoptides for biological activity of metalloproteinase inhibitor. Therefore, it is respectfully submitted that the terms "polypeptide fragment" and "polypeptide analog are not vague.

It is also stated that the term "biologically functional" in claim 25 is vague. Biologically functional clearly means a vector which has been stably tranformed with DNA capable of expressing a polypeptide having one or more biological activity of metalloproteinase inhibitor (see page 9, lines 12 to 27). As discussed above, the concept of biologically active is well understood by one of ordinary skill in the art and s not vague.

Claim 30, further stands rejected because of the use of the language "products of the expression of DNA sequences in," which it is alleged leaves it indefinite as to what polypeptide is expressed. Claim 30 has been amended to make it clear that the desired polypeptide product is a metalloproteinase inhibitor product, thereby obviating the babis for this rejection.

Accordingly, it is submitted that the claims as amended, in light of the above Remarks, are clear, definite and enabled. Consequently,

it is respectfully requested that the rejections based upon 35 U.S.C. 112 be withdrawn and claims 12 to 13, 15 to 26, 30 and 35 allowed.

35 U.S.C. 102(b), 103

Claims 12, 13, 15, 16, 18, 23 to 26, 30 and 35 stand rejected under 35 U.S.C. 102(b) as being anticipated by Doherty et al., Nature 318:66-69 (1985). It is respectfully submitted that the claims to the present invention, as amended, are not anticipated by Doherty et al. The primary structural conformation of claim 15 is specified to be a certain amino acid sequence, namely at least the amino acids 1 to 42 of Figure 2. The amino acid sequence of claim 15 therefore shows very little homology to the amino acid sequence of Doherty et al., and consequently even less homology to the nucleotide sequence disclosed in Doherty et al. Within the first 42 amino acids, only 19 are the same between the sequences, or about 45 percent homology. Therefore, there is no basis for anticipation under under 35 U.S.C. 102(b).

Claims 12, 13, 15, 16, 18, 20, 23 and 25 stand rejected under 35 U.S.C. 103 as being unpatentable over Murray et al., J. Biol, Chem. 261:4154-4159 (1986) in view of Kimmel, Methods in Enzymology 152:393-399 (1987). Murray et al. disclose a bovine collagenase inhibitor; the present invention is drawn to a human collagenase inhibitor, which although having some homology to the bovine collagenase inhibitor is a distinct protein. Moreover, the collagenase inhibitor of the present invention is not obvious over Murray et al. because one would not expect to find a human analog of the bovine collagenase inhibitor in light of the "Note Added in Proof" of Murray et al., page 4159, column 1, third full paragraph. Therein, it is suggested that the human analog of Murray et al.'s bovine collagenase inhibitor is thought to be the TIMP protein of Doherty et al., supra. This statement would clearly discourage investigators from searching for any other human collagenase inhibitors with a closer similarity to the sequence of the bovine sequence. This teaching away of Murray et al. would therefore make the present

invention unexpected and nonobvious. Consequently, there would have been no motivation to combine Murray et al. with Kimmel et al.

In summary, the claims of the present invention are drawn to the DNA sequences coding for the metalloproteinase inhibitor protein. Although the idea of using the bovine gene to probe for the human gene may have been obvious to try, the realization of that idea would not have been obvious. It is clearly established patent law that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated." Amgen Inc. v. Chugai, 18 U.S.P.Q.2d 1016, 1021 (Fed. Cir. 1991).

Claim 17 stands rejected under 35 U.S.C. 103 as being unpatentable over Murray et al. and Kimmel et al. both in view of Dillela and Woo, Methods in Enzymology 152:199-212 (1987). Claim 17 of the present invention is drawn to the genomic equivalent of the DNA sequence coding for metalloproteinase inhibitor. As such, it is nonobvious for the same reasons discussed above. Namely, the mere existence of a human protein different from that of Doherty et al. having metalloproteinase inhibitor activity was not considered possible in light of the satement made in the "Note Added in Proof" of Murray et al., page 4159, column 1, third full paragraph. Second, even if such a protein were thought to exist, it would only be an invitation to experiment and would neither make the existence of the present invention nor its identity obvious. Consequently, there is no motivation or manner of combining Doherty et al. and/or Murray et al. and/or Kimmel et al. and/or Dillela and Woo to arrive at the DNA sequences of the present invention.

Claims 19 and 21 stand rejected under 35 U.S.C. 103 as being unpatentable over Doherty et al. taken alone or over Murray et al. and Kimmel et al. both in view of Robinson et al., Nucl. Acids Res. 12:6663-6669 (1984) and Bennetzen et al., J. Biol. Chem. 257:3026-3031 (1982). It is stated that the teaching of Robinson et al. and Bennetzen et al. teach substitution of E. coli and yeast preferred codons for the sequences of Doherty et al. or Murray et al. and

Kimmel. That is all well and good, but as discussed above, Doherty et al does not teach the DNA sequences which code for the polypeptides of the present invention and Murray et al. and Kimmel do not lead to the DNA sequences that code for metalloproteinase inhibitors. One cannot exprapolate from the cDNA sequences or the genomic sequences for a protein to the yeast and E. coli preferred DNA sequences until the amino acid sequence for the protein is determined or until the naturally occuring DNA sequence is obtained. Therefore, until the DNA sequences of claims 15 to 18 of the present invention had been obtained, the genomic DNA sequences could not have been obtained. It is not appropriate to use hindsight to allege an invention (yeast and E. coli preferred DNA sequences for metalloproteinase inhibitor) is obvious when the starting material for for that invention (the cDNA and/or genomic sequence for naturally occurring metallproteinase inhibitor) is part of the same invention. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Claim 22 stands rejected under 35 U.S.C. 103 as being unpatentable over Doherty et al. alone or over Murray et al. and Kimmel et al. both in view of Gebeyehu et al., Nucl. Acids Res. 15:4513-4534 (1987). It is stated that Gebeyhu et al. discloses a method of biotin labelling of DNA, which would make it obvious to biotin label the DNA of Doherty et al. or Murray et al. and Kimmel. Once again, as discussed above, Doherty et al. and Murray et al. and Kimmel do not teach the DNA sequences of the present invention. Therefore, until the DNA sequences of the present invention were invented by applicants, it could not have been contemplated to label them with biotin or any other label. In other words, the labelled DNA sequences of the present invention could not have been contemplated until the DNA sequences of the present invention were revealed for the forst time in the captioned application.

Accordingly, it is submitted that the pending claims of the present invention are neither anticipated nor obvious in view of the prior art. Consequently, it is respectfully requested that the rejections based upon 35 U.S.C. 102(b) and 103 be withdrawn and the claims allowed.

Applicants assert that they have invented a useful, novel and nonobvious method for inhibiting dissemination of tumor cells by administering an effective amount of specific metalloproteinase inhibitors. It is respectfully submitted that the enclosed amendments and remarks overcome the objections and rejections posed by the Examiner. Therefore, it is respectfully requested that such objections and rejections be withdrawn and claims 12 to 13, 15 to 26, 30 and 35 be allowed.

The Commissioner is authorized to charge any fees associated with this application to our Deposit Account Number 01-0519. Any questions associated with this application may be directed to applicants' attorney at (805) 499-5725, Extension 4426.

Respectfully submitted,

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